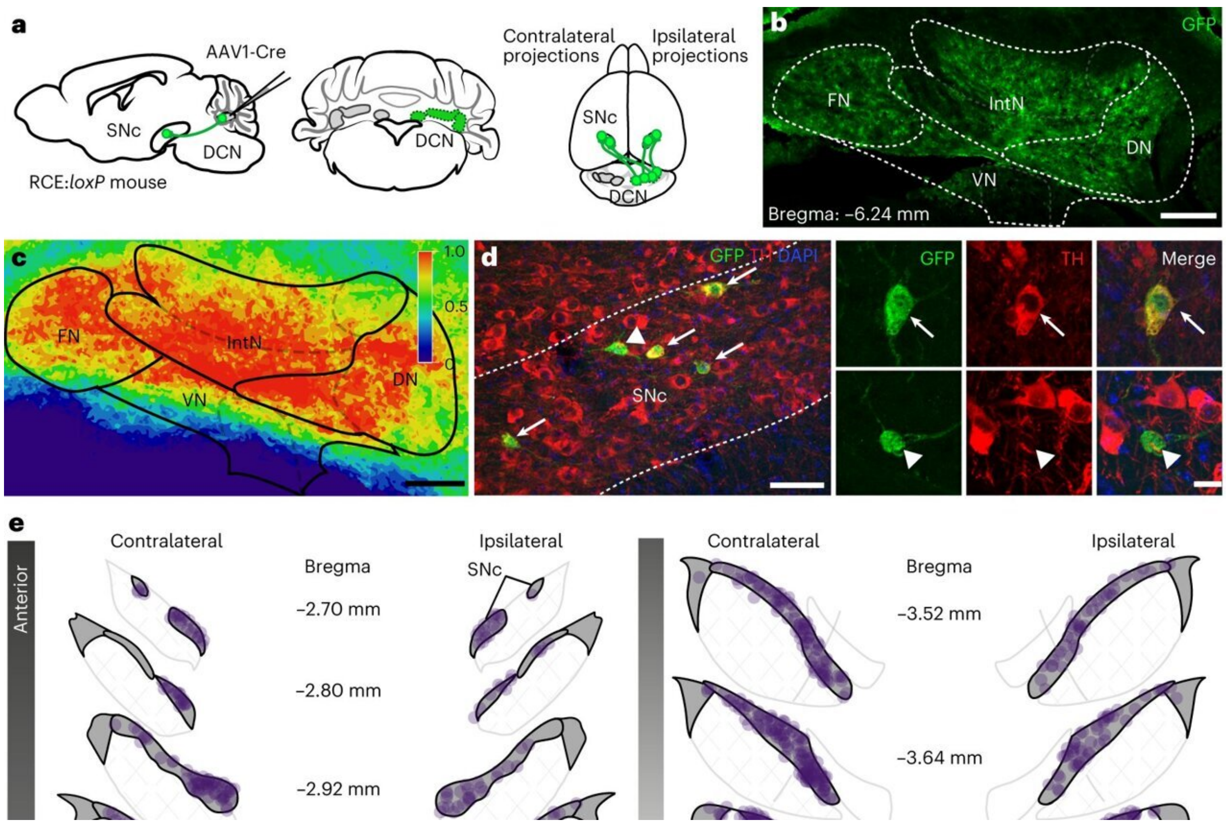
Researchers establish brain pathway linking motivation, addiction and disease

January 25 2024, by Jesse Jenkins



The cerebellum sends monosynaptic bilateral projections to the SNc. Credit: *Nature Neuroscience* (2024). DOI:10.1038/s41593-023-01560-9

New findings published in the journal *Nature Neuroscience* have shed light on a mysterious pathway between the reward center of the brain that is key to how we form habits, known as the basal ganglia, and another anatomically distinct region where nearly three-quarters of the brain's neurons reside and assist in motor learning, known as the cerebellum.

Researchers say the connection between the two regions potentially changes our fundamental view of how the brain processes voluntary movements and conditioned learning, and may lend fresh insight into the neural mechanisms underlying addiction and neurodegenerative diseases like Parkinson's.

"We are exploring a direct communication between two major components of our brain's movement system, which is absent from neuroscience textbooks. These systems are traditionally thought to function independently," said Farzan Nadim, chair of NJIT's Department of Biological Sciences, whose research is in collaboration with the Khodakhah lab at Albert Einstein College of Medicine.

"This pathway is physiologically functional and potentially affects our behaviors every day."

While both subcortical structures have long been known for their separate roles in coordinating movement through the cerebral cortex, they are also critical to both conditioned and error-correction learning.

The basal ganglia, a group of midbrain nuclei that Nadim describes as the "brain's go-no-go system" for determining whether we initiate or suppress movement, is also involved in reward-based learning of behavior triggered by the release of dopamine.

"It's the learning system that promotes motivated behavior, like studying for a good grade. It's also hijacked in cases of addiction," said Nadim, co-author of the study. "On the other hand, every behavior that we learn—whether it's to hit a baseball or play violin—this motor learning is happening in your cerebellum at the back of the brain. It's your brain's optimization machine."

However, the team's latest research suggests the cerebellum could be involved in both.

In their study, Nadim and collaborators say they have reported the first direct evidence that the two systems are intertwined—showing the cerebellum modulates basal ganglia dopamine levels that influence movement initiation, vigor of movement and reward processing.

"This connection starts at the cerebellum and goes to neurons in the midbrain that provide dopamine to the basal ganglia, called the substantia nigra pars compacta. …. We have brain recordings showing this signal is strong enough to activate the release of dopamine within the basal ganglia," explained Nadim. "This circuit may be playing a role in linking the cerebellum to motor and nonmotor dysfunctions."

The team is seeking to identify exactly where cerebellar projections to the dopamine system originate at the nuclei level, a key step in learning whether the function of this pathway can be manipulated, Nadim said.

However, the team's findings so far could have research implications for neurodegenerative diseases like Parkinson's, which is associated with the death of dopamine-producing neurons in the substantia nigra.

"This pathway seems very important to our vigor of movement and speed of cognitive processes. Parkinson's patients not only suffer from suppression of movement, but apathy in some cases," said Nadim. "The cerebellum's location at the back of the brain makes it a much easier target for novel therapeutic techniques, such as non-invasive transmagnetic or direct-current stimulation.

"Since we've shown the cerebellum is directly exciting dopamine neurons in the substantia nigra, we might now use mouse models for Parkinson's to explore such techniques to see if that jumpstarts activity of these neurons and relieves symptoms of the disease."

More information: Washburn, S. et al, The cerebellum directly modulates the substantia nigra dopaminergic activity *Nature Neuroscience* (2024). DOI: 10.1038/s41593-023-01560-9. www.nature.com/articles/s41593-023-01560-9

Provided by New Jersey Institute of Technology